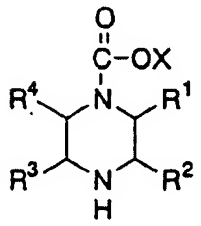
In the Specification

Please replace paragraph [0010] with the following:

Furthermore, the piperazine derivative can be in a free state or can also form a salt. Examples of it include tartaric ~~acids~~acid salts such as p-, p'-ditoluoyltartaric acid (PTTA) salt, o-, o'-ditoluoyltartaric acid (OTTA) salt, dibenzoyltartaric acid (DBTA) salt, and p-, p'-dianisoyl-tartaric acid (DATA) salt, benzoic ~~acids~~acid salts such as benzoic acid salt, 3,5-dinitrobenzoic acid salt and 1,3-benzenedicarboxylic acid salt, mineral acid salts such as phenol salts, hydrochloric acid salts, sulfuric acid salts, nitric acid salts and phosphoric acid salts of phenol, nitrophenol, resorcinol, catechol, etc., metal halide salts such as copper tetrachloride salt, copper tetrabromide salt and cobalt trichloride salt, etc. Preferred is a salt of tartaric acid and any of its derivatives, and more preferred is a salt of optically active tartaric acid and any of its derivatives.

Please replace paragraph [0011] with the following:

Now, the oxycarbonyl-substituted piperazine derivative obtained in this invention is represented by general formula (2):



(2)

(where R^1, R^2, R^3 and R^4 denote, respectively independently, i) a hydrogen atom, ii) an alkyl group with 1 to 4 carbon atoms, iii) an alkoxy group with 1 to 4 carbon atoms, iv) a halogen group, v) a carboxyl group, vi) a carbamoyl group, or vii) an N-alkylcarbamoyl group with 1 to 4 carbon atoms in its alkyl group; X denotes i) an alkyl group with 1 to 4 carbon atoms, ii) an alkenyl group with 2 to 4 carbon atoms, iii) an alkynyl group with 2 to 4 carbon atoms, iv) an aralkyl group not substituted in

the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group, or v) an aryl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group; excluding the case where all of R^1, R^2, R^3 and R^4 denote a hydrogen atom respectively), and it is preferred that X denotes a tert-butyl group or benzyl group. Examples include 1-methoxycarbonyl-2-methylpiperazine, 1-methoxycarbonyl-3-methylpiperazine, 2-ethyl-1-methoxycarbonylpiperazine, 1-ethoxycarbonyl-2-methylpiperazine, 1-tert-butoxycarbonyl-2-methylpiperazine, 1-tert-butoxycarbonyl-3-methylpiperazine, 1-tert-butoxycarbonyl-2,3-dimethylpiperazine, 1-tert-bu-toxycarbonyl-2-methoxy-3-methylpiperazine, 1-vinyloxycarbonylpiperazine, 1-vinyl-2-methylpiperazine, 1-vinyl-3-methylpiperazine, 1-allyloxycarbonylpiperazine, 1-allyloxycarbonyl-2-methylpiperazine, 1-allyloxycarbonyl-3-methylpiperazine, 1-~~methylpropinyloxycarbonyl~~ methylpropionyloxycarbonyl-2-methylpiperazine, 1-benzyloxycarbonyl-2-piperazine, 1-benzyloxycarbonyl-3-methylpiperazine, 1-benzyloxycarbonyl-2,3-dimethylmethylpiperazine, 1-benzyloxycarbonyl-3,5-dimethylpiperazine, 1-benzyloxycarbonyl-3-methoxypiperazine, 1-(p-methylphenylmethyl)oxycarbonyl-2-methylpiperazine, 1-(p-methylphenylmethyl)oxycarbonyl-3-methylpiperazine, 1-phenoxy-carbonyl-2-methylpiperazine, 1-phenoxycarbonyl-2-methylpiperazine, 1-phenoxycarbonyl-3-methylpiperazine, 1-phenoxycarbonyl-2,5-dimethylpiperazine, etc. These compounds can be synthesized from general formula (1), and can be either racemic modifications or optically active substances.

Please replace paragraph [0022] with the following:

The nitrogen-containing compound made to coexist is not especially limited. Examples include pyridine, α-picoline, β-picoline, γ-picoline, 2-ethylpyridine, 3-ethylpyridine, 4-ethylpyridine, 2-n-propylpyridine, 3-n-propylpyridine, 4-n-propylpyridine, 2-isopropylpyridine, 2-phenylpyridine,

2-vinylpyridine, 3-aminopyridine, 2-hydroxypyridine, 2-methoxy-pyridine, 2-~~chloropyrodine~~chloro-pyridine, 3-fluoropyridine, 4-bromopyridine, 3-iodopyridine, 2-formylpyridine, 3-acetylpyridine, 2-pyridinecarboxylic acid, methyl 3-pyridinecarboxylate, 3-pyridinecarboxylic acid amide, 2-cyanopyridine, 3-nitropyridine, pyrrole, indole, pyrazole, isoxazole, isothiazole, indazole, imidazole, oxazole, thiazole, benzimidazole, quinoline, isoquinoline, pyridazine, pyrimidine, pyrazine, quinoxaline, carbazole, α-aminonaphthalene, β-amino-naphthalene, aniline, 2,6-lutidine, trimethylamine, etc. Preferred are aromatic nitrogen-containing compounds, and further preferred are aromatic nitrogen-containing compounds with a pKa of 7 or less. Especially preferred are pyridine and its derivatives.

Please replace paragraph [0023] with the following:

The pKa values of some nitrogen-containing compounds are shown below. Handbook of Chemistry, Eleventh Edition (~~McGROW~~McGRAW-HILL Book Company, 1973) and Hetero-kan Kagobutsu-no Kagaku (= Chemistry of Heterocyclic Compounds) (Kodansha Scientific, 1988) show 5.23 for pyridine, 6.62 for 2-methoxypyridine, 0.72 for 2-~~chloropyrodine~~chloropyridine, 2.5 for pyrazole, 10.7 for trimethylamine and 7.76 for triethanolamine.

Please replace paragraph [0083] with the following:

The organic solvent used in the washing step is not especially limited if it is industrially available, but considering the recovery rate of the oxycarbonyl-substituted piperazine derivative at the time of extraction, an organic solvent of 10% or less in the mutual solubility with water at 20°C is preferably used. Examples include aromatic hydrocarbons such as toluene, benzene, o-xylene, m-xylene, p-xylene and ethylbenzene, alcohols such as 1-butanol, 2-butanol, isobutanol, 1-pentanol, 2-pentanol, 3-pentanol, 1-hexanol and cyclohexanol, ethers such as diethyl ether, ethyl propyl ether, ethyl isopropyl ether, isopropyl ether, isobutyl methyl ether, tert-butyl methyl ether and

tetrahydrofuran, ketones such as 3-pentanone, tert-butyl methyl ketone, 2-hexanone, 3-hexanone and 2-heptanone. Preferred are aromatic hydrocarbons and alcohols, and more preferred are aromatic hydrocarbons. Especially preferred is toluene.

Please replace paragraph [0109] with the following:

In this invention, the contents of the impurities represented by the general formulae (5) to (8) contained in the reaction solution containing the oxycarbonyl-substituted piperazine derivative can be obtained in reference to the total amount of the impurities represented by the general formula (5) to (8) and the oxycarbonyl-substituted piperazine derivative represented by the general formula (2), i.e., from the following calculation formula {~~A1~~(A2 + A3 + A4 + A5)/(A1 + A2 + A3 + A4 + A5) x 100(%), wherein A1, A2, A3, A4 and A5 respectively denote the area percentage of the oxycarbonyl-substituted piperazine derivative represented by the general formula (2), the area percentage of the impurity represented by the general formula (5), the area percentage of the impurity represented by the general formula (6), the area percentage of the impurity represented by the general formula (7) and the area percentage of the impurity represented by the general formula (8). Similarly the contents of the respective impurities can be obtained. ~~For example, the total of the impurities contained in the reaction solution containing the oxycarbonyl-substituted piperazine derivative represented by the general formula (2) can be obtained from {A2/(A1 + A2 + A3 + A4 + A5)} x 100(%).~~

Please replace paragraph [0113] with the following:

The analytical conditions for the Z-protection reaction and Boc-protection reaction of 2-methylpiperazine are shown below.

1) Analysis of Z-protection reaction composition

Model: Shimadzu LC-10Vp

Column: Capcellpak C18, 120 angstroms, 5 μm, 4.6 mm x 250 mm (Shiseido)

Mobile phase: 5 mM sodium dodecyl sulfate aqueous solution (adjusted to pH 2.5 using phosphoric acid)/CH_3CN = 69/31 (0-15 min), 55/45 (25-40 min)

Flow rate: 1.0 ml/min

Temperature: 40°C

Detector: UV (210 nm)

Retention times:

2.7 min ... benzyl alcohol {corresponding to general formula (8)}

21.1 min ... 1-benzyloxycarbonyl-3-methylpiperazine

15.9 min ... toluene (washing solvent)

30.0 min ... 1-benzyl-4-benzyloxycarbonyl-2-methylpiperazine

31.0 min ... 1-benzyl-2-methylpiperazine

31.0 min ... 1,4-bis(benzyloxycarbonyl)-2-methylpiperazine

Please replace paragraph [0115] with the following:

The conversion and selectivity of 1-tert-butoxycarbonyl-3-methylpiperazine by the Boc-protection reaction were calculated from the following formulae using the GC area value of the peak attributable to 2-methylpiperazine and/or ~~2-methylpiperazine~~1-tert-butoxycarbonyl-3-methylpiperazine derivatives on the GC analysis chart.

Conversion = [1 – {Area value of 2-methylpiperazine in the reaction solution}/{Area value of 2-methylpiperazine in the reaction solution + Area value of 1-tert-butoxycarbonyl-3-methylpiperazine + Area value of 1-tert-butoxycarbonyl-2-methylpiperazine + Area value of 1,4-bis-(tert-butoxycarbonyl-2-methylpiperazine)}] x 100 (%)

Selectivity = (Area value of 1-tert-butoxycarbonyl-3-methylpiperazine in the reaction solution)/{Area value of 1-tert-butoxycarbonyl-3-methylpiperazine + Area value of 1-tert-butoxy-carbonyl-2-methylpiperazine + Area value of 1,4-bis(tert-butoxycarbonyl-2-methylpiperazine)} x 100(%)

Please replace paragraph [0134] with the following:

Example 5

A reaction was carried out as described for Example 1, except that the solvent was changed from ~~44.7 g~~44 g of 1-butanol to a mixed solvent consisting of 5.3 g of water and 40 g of 1-butanol (water content 10.6 wt%). After stirring at 0 to 5°C for 2 hours, the reaction solution was analyzed. As a result, the reaction yield of 1-benzyloxycarbonyl-3-methylpiperazine was 82.1% (based on the amount of 2-methylpiperazine).

Please replace paragraph [0138] with the following:

Comparative Example 4

A 200 ml four-neck flask with a pH meter and dropping funnel was charged with 10.02 g (= 0.100 mole) of racemic 2-methylpiperazine, and 50.0 g of 1-butanol was added for dissolution, being followed by addition of 50.1 g of water (water content 50.0 wt%). With vigorous stirring, benzyl chlorocarbonate was added dropwise. In this case, 48 wt% sodium hydroxide aqueous solution was added dropwise to keep the pH value of the system at 10 to 11, and as required, the system was cooled with ice to keep the internal temperature at 23 to 26°C (final water content 52.1 wt%). After completion of dropwise addition, with vigorous stirring, aging was carried out for 2 hours. The reaction solution was sampled and analyzed, and as a result, the reaction yield of 1-benzyloxycarbonyl-[[2]]3-methylpiperazine was 40.1%.

Please replace paragraph [0139] with the following:

Comparative Example 5

A 200 ml four-neck flask with a pH meter and dropping funnel was charged with 10.02 g (= 0.100 mole) of racemic 2-methylpiperazine, and 80.2 g of 1-butanol was added for dissolution, being followed by addition of 20.1 g of water (water content 20.0 wt%). With vigorous stirring, benzyl chlorocarbonate was added dropwise. In this case, 48 wt% sodium hydroxide aqueous solution was added dropwise to keep the pH value of the system at 7.5 to 8.5, and as required, the system was cooled with ice to keep the internal temperature at 23 to 26°C (final water content 23.0 wt%). After completion of dropwise addition, with vigorous stirring, aging was carried out for 2 hours. The reaction solution was sampled and analyzed, and as a result, the reaction yield of 1-benzyloxycarbonyl-[[2]]3-methylpiperazine was 50.4%.

Please replace paragraph [0151] with the following:

Comparative Example 11

A 200 ml four-neck flask with a pH meter and dropping funnel was charged with 10.22 g (= 0.102 mole) of racemic 2-methylpiperazine, and 80.5 g of 1-butanol was added for dissolution, being followed by addition of 27.5 g of water (water content 25.4 wt%). With vigorous stirring, benzyl chlorocarbonate was added dropwise. In this case, 48 wt% sodium hydroxide aqueous solution was added dropwise to keep the pH value of the system at 8 to 9.5, and as required, the system was cooled with ice to keep the internal temperature at 23 to 26°C (final water content 26.9 wt%). After completion of dropwise addition, with vigorous stirring, aging was carried out for 2.5 hours. The reaction solution was sampled and analyzed, and as a result, the conversion of 2-methylpiperazine was 89.6%, and the selectivity of 1-tert-butoxycarbonyl-3-methylpiperazine was 73.5% (reaction yield 65.9%).

Please replace paragraph [0166] with the following:

The obtained compound was analyzed. As a result, the intended 1-benzyloxycarbonyl-3-methylpiperazine accounted for 99.7 area %. The impurities showed 0.03 area % for benzyl alcohol, 0.12 for 1-benzyl-4-benzyloxycarbonyl-2-methylpiperazine, 0.08 area % for 1-benzyl-2-methylpiperazine and no detection for 1,4-dibenzyloxycarbonyl-2-methylpiperazine (for solvent toluene either). Therefore, the total of impurities was 0.23 ~~wt%~~area%. Furthermore, the optical purity was 99.4%ee.